REMARKS

Claims 57-81 and 83-104 are currently pending in the subject application. Claim 84 is withdrawn from consideration by the Examiner under 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention. Claims 57-81, 83 and 85-103 are currently under consideration and stand rejected under 35 USC §§102, 103 and 112 based on a number of positions laid out in detail in the 9/5/03 Final Office Action. Applicant respectfully disagrees with the conclusions set forth in that office action. However, in order to expedite prosecution of a portion of their invention of particular current interest, Applicant has presented a set of more narrowly focused amended claims on pages 2-16 of this paper (See also attached Appendix A). Specifically, Applicant has canceled claims 61 and 62, and has amended claims 57-59, 63-65 and 81. All the other claims remain unchanged. Below we address each of the rejections stated in the Office Action as if it were applied to the newly amended claims.

The deletion of any claims and any other loss of claimed subject matter is being made solely to expedite prosecution of the subject matter now claimed, rather than in acquiescence to any positions taken by the Examiner. In fact, Applicant is *not* acquiescing to any of those positions and is submitting this amendment without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper. Applicant explicitly reserves the right to pursue this subject matter in divisional or continuation applications.

Amendments to Claims

Claims 57-59, 64, 65 and 81, as amended, recite an antibody. Support for this amendment can be found, for example, in (now canceled) claims 61 and 62. Claim 63 has been amended to correct claim dependency, rendered necessary by cancellation of claims 61 and 62.

In addition, claim 58 has been amended to replace "wherein seconds are thirds" with "wherein the second antibody is a third antibody". No new matter is being introduced with these amendments.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 62 under 35 U.S.C. § 112, second paragraph and states that claim 62 recites a limitation on a "third ligand" which the Examiner alleges does not have

antecedent basis in claim 58 from which it depends. Without conceding the correctness of the Examiner's position, but solely in an effort to expedite prosecution, Applicant has amended claim 58 to change the language "*wherein seconds are thirds*" to "*wherein the second antibody is a third antibody*." Therefore, the stated rejection is now moot.

In view of the amendments detailed above, Applicant asserts that the claims, as amended, particularly point out and distinctly claim the invention, and respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102-103 and 104 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Photiou *et al.* (European Journal of Cancer, 33(3):463-470, March 1997). Specifically, the Examiner states that Photiou *et al.* disclose a cell-based assay in high-throughput format, citing second column lines 13-21 on page 464.

Applicant notes that the section of the Photiou *et al.* reference that the Examiner is referring to relates to a cell growth inhibition assay whereby "cells were seeded at 3000 cells/well/100 μl in 96-well flat-bottomed plates". Applicant fails to find any description on page 464, second column, lines 13-21 of the photiou *et al.* reference of a high-throughput assay comprising steps of introducing into each of a plurality of reaction vessels (i) a plurality of cells, (ii) one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated, and (iii) *an antibody that associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process*; and (iv) *assaying for antibody-component association in the reaction vessels*; wherein the plurality of reaction vessels comprises at least 96 reaction vessels. If Applicant is mistaken, the Examiner is invited to point out where, in the section entitled "Isobologram method" on page 464, second column, lines 13-21, is found any reference to an antibody that associates intracellularly with a biological component or a step of assaying for antibody-component association in the reaction vessels (*e.g.*, wells).

Absent an explicit description of the presently claimed invention in the Photiou *et al.* reference (*i.e.*, including ***all*** the claim limitations), the cited reference cannot be held to

anticipate the instant claims. Applicant respectfully requests that the stated rejection be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Claims 57-81, 83 and 85-104 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Taylor (U.S. Patent No.: 6,103,479). Specifically, the Examiner states that Taylor discloses a high-throughput method for screening physiological response of cells to biologically active compounds, said method comprising preparing an array of cells, contacting the array of cells with a fluid delivery system to enable reagent delivery to the array of cells, conducting high-throughput screening by acquiring an image of the entire array of cells to detect signal from all wells at once to identify cells that exhibit a response, converting the signal into digital data and utilizing the digital data to determine the distribution, environment or activity of cells, citing for example column 13, lines 37-56 and Example 2 columns 19-20.

Applicant respectfully submits that Taylor's method differs from Applicant's claimed invention at least in that it does not comprise the steps of (i) introducing in the reaction vessels an antibody that associates intracellularly with a biological component; and (ii) assaying for antibody-component association in the reaction vessels.

In addition, Taylor's method comprises the step of attaching the cells to a non-uniformly chemically modified micro-patterned array (see, for example, column 8, lines 28-32 and claim 1 (d)). As a result, as detailed in column 6, lines 24-27, in Taylor's method, the *delivery of cells to the "wells" is based on specific binding* (see, also, column 12 lines 1-9).

Furthermore, Taylor's invention *uses cells that contain at least one luminescent reporter molecule* [See, for example, column 13 lines 37-56 and Example 2 columns 19-20 (cited by the Examiner), as well as the background section which focuses on the use of reporter molecules as detection methods (*e.g.*, in assays) - column 4 lines 56-67 and column 5 lines 1-67]. In other words, the cells are modified (*e.g.*, genetically engineered) so that a pre-determined indicator (*e.g.*, a fluorescent protein) is expressed in the cells under prescribed conditions. As evidenced throughout Taylor's disclosure (for example, column 6 lines 61-62, column 13 lines 37-56, Taylor's method comprises means to detect, record and analyze the luminescent signals from the luminescent reporter molecules present in the cells. Accordingly, the "reporter molecule" which

is already present in the cells prior to running the screen (*i.e.*, "internal" indicator), is used to identify cells that exhibit a response.

Applicant's claimed invention does not require a step of attaching the cells to a non-uniformly chemically modified micro-patterned array, nor does it use reporter molecules as means of detection.

In light of the above remarks, the Taylor reference cannot anticipate the claimed invention. Applicant respectfully requests that the stated rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 89-101 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any one or more of Walsh (U.S. patent 5,990,092), Photiou *et al.* (European Journal of Cancer, 33(3):463-470, March 1997), Juan *et al.* (Experimental Cell Research, 239:104-110, February 1988), Claycomb (U.S. patent 6,316,207 B1; PCT published May 1998) and the Final Conference Program of LabAutomation '98 in San Diego, CA January 17-21, 1998, pages 99, 100, 124, 129 and 212. However, the Examiner concedes that the cited references do not explicitly teach test compounds from a combinatorial library, the release of test compounds from a solid support, *or various capacities and densities of wells in well plates*.

Applicant respectfully disagrees with the conclusions of the Examiner. Specifically, the legal standard for establishing a *prima facie* case of obviousness requires that three basic criteria be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success in the modification or in the combination; and (3) the prior art reference must teach all the claim limitations. All three requirements must be met to establish a *prima facie* case of obviousness. In addition, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (MPEP 706.02(j)).

Applicant maintains that the Examiner has failed to establish a prima facie case of obviousness because at least one the above requirements is not met.

A. *Motivation to combine*

Applicant asserts that none of the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references teach a *high-throughput* assay comprising steps of introducing into each of a plurality of reaction vessels (i) a plurality of cells, (ii) one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated, and (iii) an antibody that associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and (iv) assaying for antibody-component association in the reaction vessels; *wherein the plurality of reaction vessels comprises at least 96 reaction vessels.*

Specifically, Claycomb teaches a cell proliferation assay using BrdU labeling, where the cells are plated on coverslips in *12-well plates* in *1 ml* of suitable medium.

Photiou *et al.* teach an indirect immunofluorescence assay where the cells are plated on coverslips in *24-well plates*. Applicant reiterates that the assay involving 96-well plates in the section entitled "Isobologram method" on page 464, column 2, lines 13-21 of the Photiou *et al.* reference differs from the high throughput method of the presently claimed invention at least in that it lacks any reference to (i) an antibody that is introduced in the plurality of vessels, and bind intracellularly to a biological component of interest, or (ii) a step of assaying for antibody-component association in the reaction vessels (*e.g.*, wells).

Juan *et al.* disclose an immunocytochemical assay for pRb phosphorylation. However the reference does not provide specific teaching or suggestion to conduct the assay in high throughput format.

Similarly, the Walsh reference does not specifically teach a high-throughput screening method (*e.g.*, number of reaction vessels ≥ 96) according to the claimed invention. In fact, the *in vitro* assay of Example 4 in the Walsh reference (column 28 lines 47-57) which the Examiner refers to, describes that the "cells are fixed onto *<u>the</u> tissue culture dish* and dried overnight at 37°C and immunostained…" Thus, the method disclosed in the Walsh reference only utilizes *<u>one</u>* reaction vessel.

In summary, none of the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references teach or suggest that the cell-based assays in question can be carried out in high-throughput format (*e.g.*, with 96 or higher reaction vessels) nor do they provide any teaching or suggestion as to how this might be accomplished.

With respect to the "Final Conference Program of LabAutomation '98" reference, while the reference provides examples of the use of 96-, 384-, 1536- and 10,000-well plates in one enzymatic fluorescent kinetic assay (see page 100), Applicant fails to find any specific teaching or suggestion in that reference that these high density plates (*i.e.*, 96-, 384-, 1536- and 10,000-well plates) can be used in cell-based assays such as those described in the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references. Applicant invites the Examiner to specifically point out where in the "Final Conference Program of LabAutomation '98" reference may be found specific teaching or suggestion that the aforementioned high density plates may be used in a high-throughput assay comprising steps of introducing into each of a plurality of reaction vessels (i) a plurality of cells, (ii) one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated, and (iii) an antibody that associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and (iv) assaying for antibody-component association in the reaction vessels.

In summary, none of the cited references provide any specific teaching or suggestion to modify or combine the teachings of "Final Conference Program of LabAutomation '98" reference and any one or more of the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references to achieve the claimed invention. Absent any such teaching or suggestion in any of the cited references, the stated combination of references cannot be held to render obvious the claimed invention.

B. ***Reasonable expectation of success***

Applicant contends that the report of the mere existence of high-density plates (*e.g.*, 96-, 384-, 1536- and 10,000-well plates) in the "Final Conference Program of LabAutomation '98" reference does not, and cannot be held to, imply or suggest that they can *successfully* be used for any cell-based assay known in the art at the time (*e.g.*, cell-based assays disclosed for example in the Walsh, Photiou *et al.*, Juan *et al.* and/or Claycomb references). Applicant reiterates that the example described on page 159 of the "Final Conference Program of LabAutomation '98" reference supports this position. Specifically, despite the existence of 96-, 384-, 1536- and 10,000-well plates at the time, Henderson *et al.* were only able to develop a *24-well* system for the cell-based assay in question. This reinforces the statement on page 159 first paragraph that "*some cell-based assays remain difficult to automate.*" Therefore, even if there were suggestion

or teaching in any one of the cited references to combine the teachings of the "Final Conference Program of LabAutomation '98" reference with the teachings of any one or more of the Walsh, Photiou *et al.*, Juan *et al.* and/or Claycomb references, there would be no reasonable expectation of success in the combination.

The Examiner invokes the reference to "significant advantages in both cost and speed" found on page 99 of the "Final Conference Program of LabAutomation '98" reference to support a finding of reasonable expectation of success. Applicant respectfully submits that "advantages" related to speed and cost have little to do with expectation of success. As discussed above, the mere existence of high-density plates does not imply or suggest that they can *successfully* be used for any cell-based assay known in the art at the time. In fact, the "Final Conference Program of LabAutomation '98" reference specifically teaches that automation of cell-based assays can be difficult (see, for example, page 159). Therefore, the Examiner's assertion that the skilled practitioner would have been motivated to combine the cited references because there is reasonable expectation of success is simply unfounded.

Accordingly, Applicant maintains that the Examiner has applied an improper "obvious to try" rationale because there is no reasonable expectation of success in the combination of the cited references.

In view of the remarks above, Applicant respectfully submits that the Examiner has failed to establish a *Prima Facie* case of obviousness, because there is no teaching or suggestion in any of the cited references to modify or combine the teachings of any one or more of the Walsh, Photiou *et al.*, Juan *et al.*, and/or Claycomb references and the teachings of the Final Conference Program of LabAutomation '98 reference to achieve the claimed invention, and there is no expectation of success in the combination. Therefore, claims 89-101 cannot be held obvious over any one or more of Walsh, Photiou *et al.*, Juan *et al.*, Claycomb in view of the Final Conference Program of LabAutomation '98 reference. Applicant respectfully requests that the stated rejection be withdrawn.

In light of the foregoing Remarks, Applicant respectfully submits that the present case is in condition for allowance. A Notice to that effect is respectfully requested. Applicant thanks the Examiner for careful review and consideration of this case, and if the Examiner believes that a

telephone interview would be of assistance in advancing the prosecution of this application, the Examiner is invited to telephone the undersigned (617) 248-5150.

It is believed that no fee is required in connection with the filing of this Amendment. However, if Applicant is mistaken, the Commissioner is hereby authorized to charge any additional fee(s) deemed necessary to Deposit Account No. 03-1721.

Respectfully submitted,
CHOATE, HALL, & STEWART

Date: November 5, 2003

Nadège M. Lagneau, Ph.D.
Agent for Applicant
Registration. No. 51,908

PATENT GROUP
CHOATE, HALL, & STEWART
Exchange Place
53 State Street
Boston MA 02109
Telephone: 617-248-5150
Facsimile: 617-248-4000

- APPENDIX A –

CLAIMS AS PENDING AFTER ENTRANCE OF THE PRESENT AMENDMENT

57. A high-throughput method for screening one or more test compounds to identify those that exert an effect on an intracellular biological or chemical process, the method comprising steps of:

a. introducing into each of a plurality of reaction vessels:

a plurality of cells; and

one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated;

b. introducing into each of the reaction vessels an antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and

c. assaying for antibody-component association in the reaction vessels;

wherein the plurality of reaction vessels comprises at least 96 reaction vessels.

58. A high-throughput method for screening one or more test compounds; said method comprising steps of:

a. introducing into each of a plurality of reaction vessels:

a plurality of cells; and

one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated;

b. introducing into each of the reaction vessels a first antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process;

c. assaying for association between the first antibody and the component in the reaction vessels;

d. repeating step a;

e. introducing into each of the reaction vessels a second antibody characterized in that it associates intracellularly with a biological component whose presence or

amount reveals the effect of a given test compound on the biological or chemical process;

f. assaying for association between the second antibody and the component in the reaction vessels;

g. optionally repeating steps d-f, wherein the second antibody is a third antibody; and

h. retaining the information as a functional fingerprint;

wherein the plurality of reaction vessels comprises at least 96 reaction vessels.

59. The method of claim 57 or 58 further comprising the step of removing unassociated antibody from each reaction vessel.

60. The method of claim 57 or 58 wherein the biological component is a direct participant in or a product of the biological or chemical process.

63. The method of claim 57 or 58 wherein the antibody is conjugated to horseradish peroxidase.

64. The method of claim 57 wherein the method further comprises introducing a secondary ligand that binds specifically to said first antibody, and wherein the step of assaying comprises assaying for bound secondary ligand.

65. The method of claim 58 wherein the method further comprises introducing a secondary ligand that binds specifically to said first, second or third antibody, and wherein each step of assaying comprises assaying for bound secondary ligand.

66. The method of claim 64 or 65 wherein in the step of assaying, the secondary ligand is assayed intracellularly.

67. The method of claim 64 or 65 wherein the secondary ligand is an antibody.

68. The method of claim 67 wherein the antibody is conjugated to horseradish peroxidase.

69. The method of claim 57 or 64 wherein the step of assaying utilizes a detection technique selected from the group consisting of: chemiluminescence, fluorescence, phosphorescence, radioactivity, colorimetry, Ultra-Violet spectroscopy, and Infra-Red spectroscopy.

70. The method of claim 58 or 65 wherein each step of assaying independently utilizes a detection technique selected from the group consisting of: chemiluminescence, fluorescence, phosphorescence, radioactivity, colorimetry, Ultra-Violet spectroscopy, and Infra-Red spectroscopy.

71. The method of claim 57 or 58 wherein, in the step of introducing the cells in each of the plurality of reaction vessels, the cells adhere to the reaction vessel surface.

72. The method of claim 57 or 58 further comprising the step of providing one or more solutions containing at least one reagent characterized in that, when contacted with the cells, it perturbs or functions as an indicator of the intracellular biological or chemical process.

73. The method of claim 72 further comprising the step of contacting the cells with the one or more solutions under suitable conditions for the reagent to perturb or function as an indicator of the intracellular biological or chemical process in the cells.

74. The method of claim 73 wherein the intracellular biological or chemical process is DNA synthesis and the reagent comprises a natural or non-natural nucleotide.

75. The method of claim 74 wherein the reagent is 5-bromodeoxyuridine.

76. The method of claim 57 or 58 wherein the intracellular biological or chemical process is a covalent modification of an intracellular component.

77. The method of claim 76 wherein the covalent modification is an intracellular biological reaction.

78. The method of claim 77 wherein the intracellular biological reaction is nucleic acid synthesis, protein cleavage, peptide cleavage, carbohydrate addition, carbohydrate cleavage, metabolism of cellular components or synthesis of cellular components.

79. The method of claim 76 wherein the covalent modification is a post-translational event and the intracellular component is a protein.

80. The method of claim 79 wherein the post-translational event is protein glycosylation, methylation, lipidation, isoprenylation, ubiquitination, phosphorylation or acetylation.

81. The method of claim 79 wherein the antibody interacts with the post-translationally modified protein.

83. The method of claim 57 or 58 wherein the cells are from the same cell –line.

84. The method of claim 57 or 58 wherein the cells are from a plurality of cell –lines.

85. The method of claim 57 or 58 wherein at least a subset of the cells comprises a eukaryotic cell.

86. The method of claim 57 or 58 wherein at least a subset of the cells comprises a mammalian cell.

87. The method of claim 57 or 58 wherein at least a subset of the cells comprises a human cell.

88. The method of claim 57 or 58 wherein at least one test compound is from a synthetic source.

89. The method of claim 88 wherein the test compounds are from a combinatorial library.

90. The method of claim 89 wherein the test compounds are covalently bound on a solid support, the method further comprising the step of dissociating the test compounds from the solid support.

91. The method of claim 57 or 58 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 200 microliters.

92. The method of claim 57 or 58 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 50 microliters.

93. The method of claim 57 or 58 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 2 microliters.

94. The method of claim 57 or 58 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 250 nanoliters.

95. The method of claim 57 or 58 wherein the reaction vessels are arranged in a two-dimensional array with sufficient density that the center-to-center distance between adjacent vessels is less than about 8.5 millimeters.

96. The method of claim 57 or 58 wherein the reaction vessels are arranged in a two-dimensional array with sufficient density that the center-to-center distance between adjacent vessels is less than about 4.5 millimeters.

97. The method of claim 57 or 58 wherein the reaction vessels are arranged in a two-dimensional array with sufficient density that the center-to-center distance between adjacent vessels is less than about 2.25 millimeters.

98. The method of claim 57 or 58 wherein the reaction vessels are arranged in a two-dimensional array with sufficient density that the center-to-center distance between adjacent vessels is less than about 1 millimeter.

99. The method of claim 57 or 58 wherein the number of reaction vessels is greater than or equal to approximately 384 and the reaction vessels occupy a surface smaller than or equal to approximately $128 \times 86\ mm^2$.

100. The method of claim 57 or 58 wherein the number of reaction vessels is greater than or equal to approximately 1500 and the reaction vessels occupy a surface smaller than or equal to approximately $128 \times 86\ mm^2$.

101. The method of claim 57 or 58 wherein the number of reaction vessels is greater than or equal to approximately 6000 and the reaction vessels occupy a surface smaller than or equal to approximately $128 \times 86\ mm^2$.

102. The method of claim 57 or 58 wherein in the step of introducing the test compounds into the plurality of reaction vessels, the test compounds are the same or different.

103. The method of claim 57 or 58 wherein in the step of introducing the test compounds into the plurality of reaction vessels, each reaction vessel contains one test compound.

104. The method of claim 57 or 58 wherein at least one test compound is from a natural source.